

* * * * * * * * * * Welcome to STN International * * * * * * * * *

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| <u>NEWS 1</u> | Web Page URLs for STN Seminar Schedule - N. America |
| <u>NEWS 2</u> | "Ask CAS" for self-help around the clock |
| <u>NEWS 3</u> May 12 | EXTEND option available in structure searching |
| <u>NEWS 4</u> May 12 | Polymer links for the POLYLINK command completed in REGISTRY |
| <u>NEWS 5</u> May 27 | New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus |
| <u>NEWS 6</u> May 27 | CAplus super roles and document types searchable in REGISTRY |
| <u>NEWS 7</u> Jun 28 | Additional enzyme-catalyzed reactions added to CASREACT |
| <u>NEWS 8</u> Jun 28 | ANTE, AQUALINE, BIOENG, CIVILENG, ENVIROENG, MECHENG, and WATER from CSA now available on STN(R) |
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| <u>NEWS 21</u> SEP 14 | STN Patent Forum to be held October 13, 2004, in Iselin, NJ |

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| <u>NEWS EXPRESS</u> | JULY 30 CURRENT WINDOWS VERSION IS V7.01, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004 |
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| <u>NEWS INTER</u> | General Internet Information |
| <u>NEWS LOGIN</u> | Welcome Banner and News Items |
| <u>NEWS PHONE</u> | Direct Dial and Telecommunication Network Access to STN |
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* * * * * * * * * * STN Columbus * * * * * * * * * * *

FILE 'HOME' ENTERED AT 20:49:15 ON 15 SEP 2004

| => file hcaplus
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|------------------|---------------|
|---|------------------|---------------|

| | | |
|---------------------|------|------|
| FULL ESTIMATED COST | 0.21 | 0.21 |
|---------------------|------|------|

FILE 'HCAPLUS' ENTERED AT 20:49:22 ON 15 SEP 2004
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FILE COVERS 1907 - 15 Sep 2004 VOL 141 ISS 12
 FILE LAST UPDATED: 14 Sep 2004 (20040914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s antiarrhythmic? {} atrial } fibrillation
 UNMATCHED RIGHT PARENTHESIS 'ATRIAL) FIBRILLAT'
 The number of right parentheses in a query must be equal to the number of left parentheses.

=> s antiarrhythmic? () atrial {} fibrillation
 13326 ANTIARRHYTHMIC?
 22231 ATRIAL
 1 ATRIALS
 22231 ATRIAL
 (ATRIAL OR ATRIALS)
 8211 FIBRILLATION
 173 FIBRILLATIONS
 8311 FIBRILLATION
 (FIBRILLATION OR FIBRILLATIONS)
 L1 62 ANTIARRHYTHMIC? (W) ATRIAL (W) FIBRILLATION

=> s l1 and potassium {} block?
 542006 POTASSIUM
 15 POTASSIUMS
 542008 POTASSIUM
 (POTASSIUM OR POTASSIUMS)
 527809 BLOCK?
 130 POTASSIUM (W) BLOCK?
 L2 0 L1 AND POTASSIUM (W) BLOCK?

=> s l1 and potassium
 542006 POTASSIUM
 15 POTASSIUMS
 542008 POTASSIUM
 (POTASSIUM OR POTASSIUMS)
 L3 4 L1 AND POTASSIUM

=> s 13 and review/dt
 1757748 REVIEW/DT

term sinus rhythm maintenance in flutter than AF. The relative specificity of class I and III AADs for flutter is explained by the newer concepts of arrhythmia mechanisms. Class III AADs would prolong refractory period without affecting conduction velocity, thus increasing wavelength.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s antiarrhythmic? () supraventricular () arrhythmia?

13326 ANTIARRHYTHMIC?

658 SUPRAVENTRICULAR

14787 ARRHYTHMIA?

L7 1 ANTIARRHYTHMIC? (W) SUPRAVENTRICULAR (W) ARRHYTHMIA?

=> s l7 and review/dt

1757748 REVIEW/DT

L8 1 L7 AND REVIEW/DT

=> d 18, ibib abs, 1

L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Series
 Text References

ACCESSION NUMBER: 1996:159635 HCAPLUS
 DOCUMENT NUMBER: 124:277460
 TITLE: Current topics on new class III antiarrhythmic drugs:
 In special reference to clinical effects on
 supraventricular arrhythmias
 Iinuma, Hiroyuki; Kato, Kazuo
 CORPORATE SOURCE: Cardiovascular Institute, Tokyo, Japan
 SOURCE: Recent Progress in Electropharmacology of the Heart,
 Proceedings of the International Satellite Symposium
 of the 59th Annual Scientific Meeting of the Japanese
 Circulation Society, Nagoya, Apr. 3-4, 1995 (1996),
 Meeting Date 1995, 161-7. Editor(s): Toyama, Junji;
 Hiraoka, Masayasu; Kodama, Itsuo. CRC: Boca Raton,
 Fla.
 CODEN: 62LYAD
 DOCUMENT TYPE: Conference; General Review
 LANGUAGE: English
 AB A review with 2 refs.

=> s antiarrhythmic? and cardiac () arrhythmia?

13326 ANTIARRHYTHMIC?

101846 CARDIAC

48 CARDIACS

101871 CARDIAC

(CARDIAC OR CARDIACS)

1 ARRHYMTHIA?

0 CARDIAC (W) ARRHYMTHIA?

L9 0 ANTIARRHYTHMIC? AND CARDIAC (W) ARRHYMTHIA?

=> s antiarrhythmic? () cardiac? () arrhythmia?

13326 ANTIARRHYTHMIC?

103098 CARDIAC?

14787 ARRHYTHMIA?

L10 8 ANTIARRHYTHMIC? (W) CARDIAC? (W) ARRHYTHMIA?

=> s l10 and review/dt

1757748 REVIEW/DT

L11 2 L10 AND REVIEW/DT

=> d l11, bibk abs, 1-2

L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text **Cited References**

ACCESSION NUMBER: 2000:896487 HCAPLUS
 DOCUMENT NUMBER: 135:55245
 TITLE: Clamikalant (Aventis)
 AUTHOR(S): O'Rourke, Stephen T.
 CORPORATE SOURCE: Department Pharmaceutical Sciences, North Dakota State University, Fargo, ND, 58105-5055, USA
 SOURCE: IDrugs (2000), 3(11), 1353-1357
 CODEN: IDRUFN; ISSN: 1369-7056
 PUBLISHER: Current Drugs Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review with 57 refs. Clamikalant is a cardioselective blocker of the ATP-dependent potassium channel (KATP) which is under development by Aventis Pharma (formerly Hoechst Marion Roussel) for the potential treatment of cardiac arrhythmia. The sodium salt, HMR-1098, is in phase II trials. Aventis plans for an i.v. prepn. of the drug to be launched in 2004, and an oral prepn. to be available in 2005. Clamikalant prevented ischemia-induced redns. in refractory period in dogs with ventricular fibrillation without significant hemodynamic effects or alteration in blood glucose levels. HMR-1883 exerted an anti-arrhythmic effect in a model of isolated hearts from male White New Zealand rabbits, and indicated and did not interfere with post-ischemic hyperemia.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

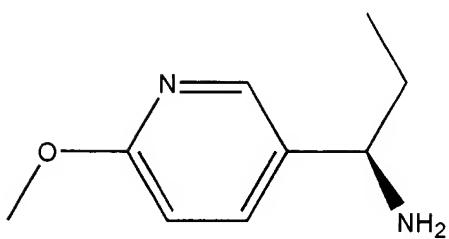
L11 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text **Cited References**

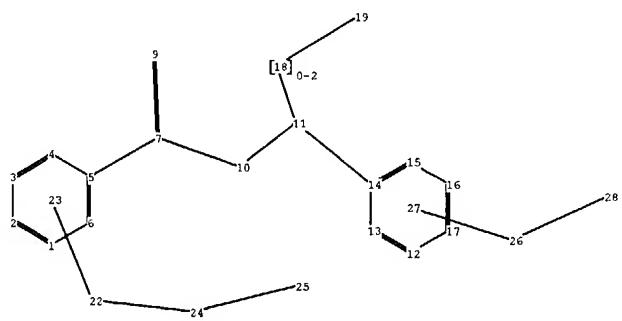
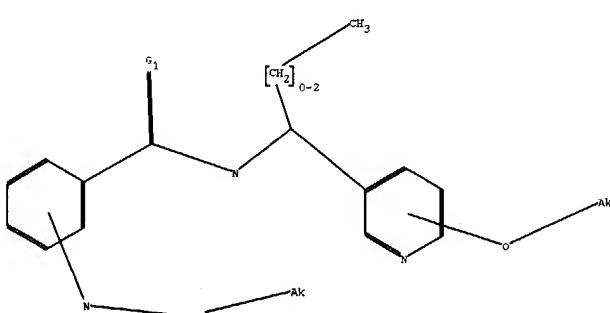
ACCESSION NUMBER: 2000:825976 HCAPLUS
 DOCUMENT NUMBER: 134:320400
 TITLE: Cardiac arrhythmias and drugs affecting intracellular calcium ions
 AUTHOR(S): Honma, Nobuo; Hashimoto, Keitaro
 CORPORATE SOURCE: Department of Pharmacology, Yamanashi Medical University, Japan
 SOURCE: Clinical Calcium (2000), 10(11), 1413-1418
 CODEN: CLCCEJ; ISSN: 0917-5857
 PUBLISHER: Iyaku Janarusha
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese

AB A review with 2 refs. In the heart, Ca²⁺ concn. and transport are closely related to elec. conduction and impulse formation, as well as to myocardial contraction. It is important to know how the an abnormality of intracellular Ca²⁺ concn. leads to cardiac arrhythmias. This review focuses on cardiac arrhythmias and drugs which potentially affect intracellular Ca²⁺ and summarizes (1) the mechanisms of arrhythmias, (2) the target proteins of drug action, and (3) the introduction of new drugs.

=>



1(R)-(6-Methoxypyridin-3-yl)propylamine



chain nodes :
7 9 10 11 18 19 22 24 25 26 28

ring nodes :

1 2 3 4 5 6 12 13 14 15 16 17

chain bonds :

5-7 7-9 7-10 10-11 11-14 11-18 18-19 22-24 24-25 26-28

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17

exact/norm bonds :

7-9 7-10 10-11 22-24 24-25 26-28

exact bonds :

5-7 11-14 11-18 18-19

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17

isolated ring systems :

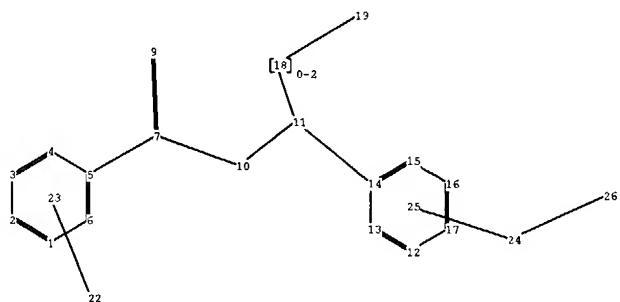
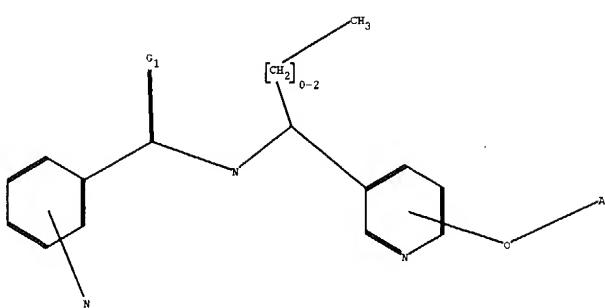
containing 1 : 12 :

G1:0,S

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 9:CLASS 10:CLASS 11:CLASS
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS 22:CLASS
23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS

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chain nodes :

7 9 10 11 18 19 22 24 26

ring nodes :

1 2 3 4 5 6 12 13 14 15 16 17

chain bonds :

5-7 7-9 7-10 10-11 11-14 11-18 18-19 24-26

ring bonds :

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normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17

isolated ring systems :

containing 1 : 12 :

G1:0,S

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 9:CLASS 10:CLASS 11:CLASS
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS 22:CLASS
23:CLASS 24:CLASS 25:CLASS 26:CLASS

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FILE 'HOME' ENTERED AT 20:32:06 ON 15 SEP 2004

| => file reg
COST IN U.S. DOLLARS | SINCE FILE
ENTRY | TOTAL
SESSION |
|-------------------------------------|---------------------|------------------|
|-------------------------------------|---------------------|------------------|

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|---------------------|------|------|
| FULL ESTIMATED COST | 0.21 | 0.21 |
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STRUCTURE FILE UPDATES: 14 SEP 2004 HIGHEST RN 744786-72-9
 DICTIONARY FILE UPDATES: 14 SEP 2004 HIGHEST RN 744786-72-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=>

L1 STRUCTURE uploaded

=> l1

L1 IS NOT A RECOGNIZED COMMAND

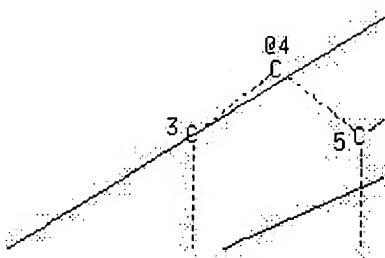
The previous command name entered was not recognized by the system.
 For a list of commands available to you in the current file, enter
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=> d l1

L1 HAS NO ANSWERS

L1 STR

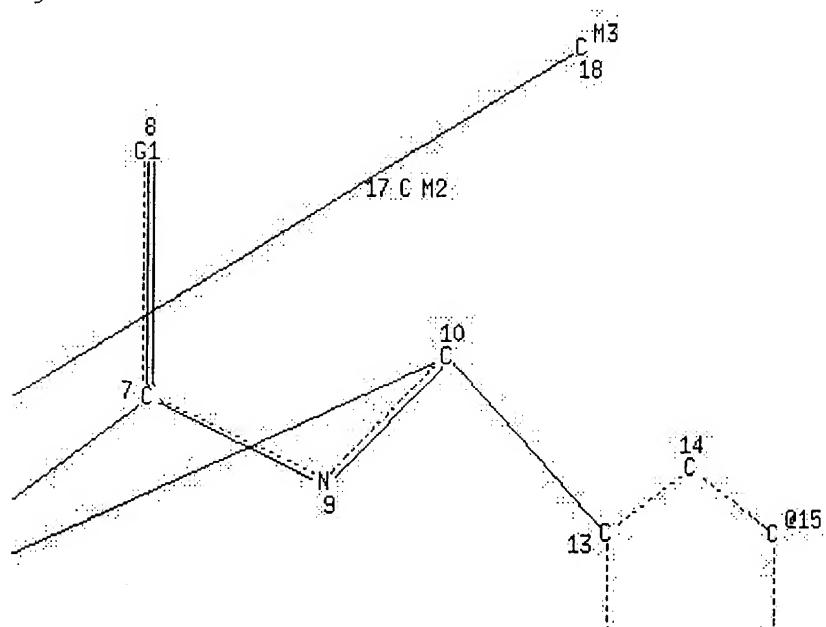
0 27 S 28



h eb c g cg b cg

eb

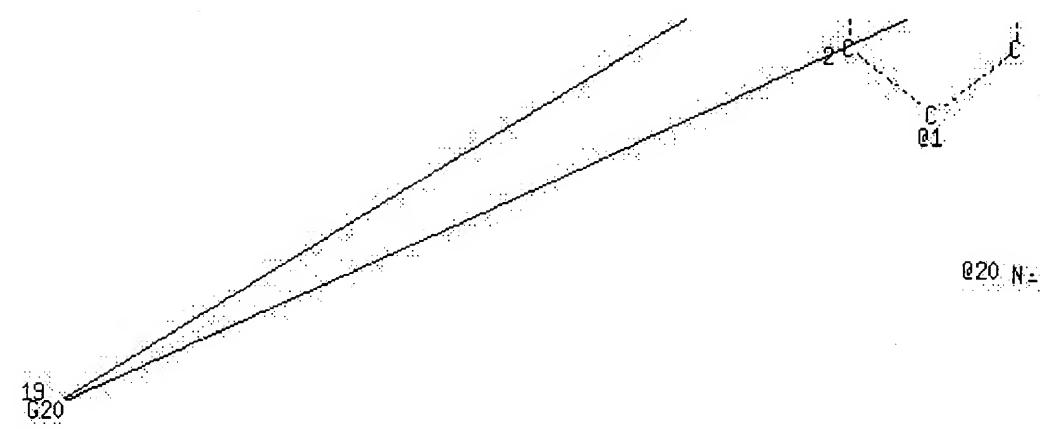
Page 1-A



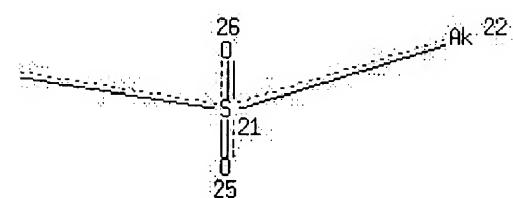
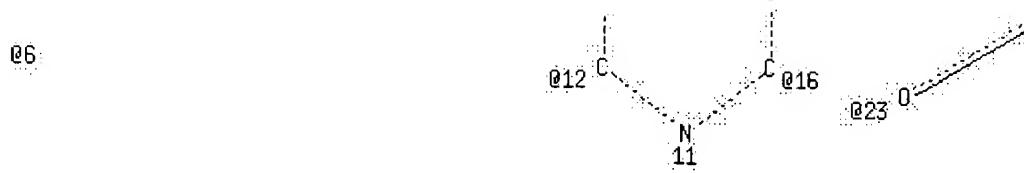
Page 1-B



Page 1-C



Page 2-A



Page 2-B

~~EB~~

h

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c

g

cg

b

cg

eb

Page 2-C
 VAR G1=27/28
 REP G20=(0-2) 17-10 17-18
 VPA 20-1/4/6 S

VPA 23-12/15/16 S
 NODE ATTRIBUTES:

| | | | |
|--------|-------|----|----|
| HCOUNT | IS M2 | AT | 17 |
| HCOUNT | IS M3 | AT | 18 |
| NSPEC | IS R | AT | 1 |
| NSPEC | IS R | AT | 2 |
| NSPEC | IS R | AT | 3 |
| NSPEC | IS R | AT | 4 |
| NSPEC | IS R | AT | 5 |
| NSPEC | IS R | AT | 6 |
| NSPEC | IS C | AT | 7 |
| NSPEC | IS C | AT | 8 |
| NSPEC | IS C | AT | 9 |
| NSPEC | IS C | AT | 10 |
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| NSPEC | IS R | AT | 13 |
| NSPEC | IS R | AT | 14 |
| NSPEC | IS R | AT | 15 |
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| NSPEC | IS C | AT | 25 |
| NSPEC | IS C | AT | 26 |

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MLEVEL IS CLASS AT 7 9 10 17 18 20 21 22 23 24 25 26 27 28

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 28

STEREO ATTRIBUTES: NONE

=> s li

SAMPLE SEARCH INITIATED 20:36:14 FILE 'REGISTRY'
 SAMPLE SCREEN SEARCH COMPLETED - 1 TO ITERATE

100.0% PROCESSED 1 ITERATIONS
 SEARCH TIME: 00.00.01

0 ANSWERS

| | | |
|------------------------|--------|--------------|
| FULL FILE PROJECTIONS: | ONLINE | **COMPLETE** |
| | BATCH | **COMPLETE** |
| PROJECTED ITERATIONS: | 1 TO | 80 |
| PROJECTED ANSWERS: | 0 TO | 0 |

L2 0 SEA SSS SAM L1

=> s li full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 20:36:18 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 23 TO ITERATE

100.0% PROCESSED 23 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

L3 1 SEA SSS FUL L1

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COST IN U.S. DOLLARS SINCE FILE TOTAL
FULL ESTIMATED COST ENTRY SESSION
157.94 158.15

FILE 'HCPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004
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FILE COVERS 1907 - 15 Sep 2004 VOL 141 ISS 12
FILE LAST UPDATED: 14 Sep 2004 (20040914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13.
L4 1 L3

=> d 14, ibib abs fhitstr, 1

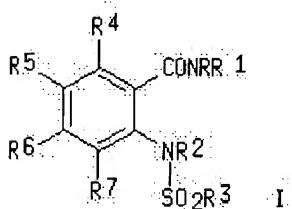
L4 ANSWER 1 OF 1 HCPLUS COPYRIGHT 2004 ACS on STN



| | |
|----------------------------|--|
| ACCESSION NUMBER: | 2002:849582 HCPLUS |
| DOCUMENT NUMBER: | 137:352782 |
| TITLE: | Preparation of anthranilic acid amides as antiarrhythmics |
| INVENTOR(S): | Brendel, Joachim; Pirard, Bernard; Peukert, Stefan;
Kleemann, Heinz-Werner; Hemmerle, Horst |
| PATENT ASSIGNEE(S): | Aventis Pharma Deutschland GmbH, Germany |
| SOURCE: | PCT Int. Appl., 111 pp. |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | German |
| FAMILY ACC. NUM. COUNT: | 1 |
| <u>PATENT INFORMATION:</u> | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-------------------------------|--|----------|-------------------------|------------|
| <u>WO 2002088073</u> | A1 | 20021107 | <u>WO 2002-EP4138</u> | 20020413 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| <u>DE 10121003</u> | A1 | 20021219 | <u>DE 2001-10121003</u> | 20010428 |
| <u>EP 1385820</u> | A1 | 20040204 | <u>EP 2002-742898</u> | 20020413 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| <u>EE 200300529</u> | A | 20040216 | <u>EE 2003-529</u> | 20020413 |
| <u>BR 2002009185</u> | A | 20040803 | <u>BR 2002-9185</u> | 20020413 |
| <u>JP 2004527557</u> | T2 | 20040909 | <u>JP 2002-585377</u> | 20020413 |
| <u>US 2003187033</u> | A1 | 20031002 | <u>US 2002-132163</u> | 20020426 |
| <u>NO 2003004751</u> | A | 20031113 | <u>NO 2003-4751</u> | 20031023 |
| <u>PRIORITY APPLN. INFO.:</u> | | | <u>DE 2001-10121003</u> | A 20010428 |
| | | | <u>WO 2002-EP4138</u> | W 20020413 |

OTHER SOURCE(S) : MARPAT 137:352782
GI



AB Title compds. [I; R = H, C1-4 alkyl, CpH2pR14, etc.; p = 0-5; R14 = cycloalkyl(substituted) (hetero)aryl; R1 = (branched) (unsatd.) (substituted) O-interrupted alkyl; R2 = H, C1-4 alkyl; R3 = C3-7 alkyl, C3-7 cycloalkyl, (substituted) naphthyl, Ph; R4-R7 = F, Cl, Br, I, CF3, OCF3, OCHF2, NO2, cyano, CO2Me, CONH2, COMe, OH, C1-4 alkyl, C1-4 alkoxy, N(Me)2, SO2NH2, NHSO2Me], were prep'd. Thus, 0.6 mmol 2-phenylsulfonylamino-5-chlorobenzoyl chloride (prepn. given) was added to a mixt. of 0.66 mmol S-(-)-1-methylbenzylamine and 0.9 mmol Et3N in CH2Cl2 followed by stirring over night at room temp. to give 61 mg (S)-2-phenylsulfonylamino-5-chloro-N-(1-phenylethyl)benzamide. I act upon the Kv1.5 potassium channel and inhibit a potassium flow described as ultra-rapidly activating delayed rectifier in the human cardiac atrium. Tested I inhibited human Kv1.5 potassium flow in oocytes of Xenopus laevis with IC50 = 0.3->10 µM. β -Blockers and IKs-channel blockers can be used for the tablet formulation.

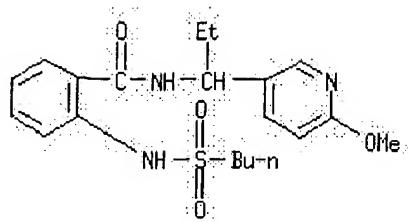
IT 474450-36-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of anthranilic acid amides as antiarrhythmics)

RN 474450-36-7 HCAPLUS

CN Benzamide, 2-[(butylsulfonyl)amino]-N-[1-(6-methoxy-3-pyridinyl)propyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file caold

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|--|------------------|---------------|
| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
| FULL ESTIMATED COST | 7.12 | 165.27 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -0.70 | -0.70 |

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FILE COVERS 1907-1966

FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> & his

(FILE 'HOME' ENTERED AT 20:32:06 ON 15 SEP 2004)

FILE 'REGISTRY' ENTERED AT 20:32:11 ON 15 SEP 2004

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 L3 1 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004

L4 1 S L3

FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004

=> s l3
 L5 0 L3

=> file reg

| | | |
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| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|--|------------------|---------------|
| CA SUBSCRIBER PRICE | 0.00 | -0.70 |

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 14 SEP 2004 HIGHEST RN 744786-72-9
 DICTIONARY FILE UPDATES: 14 SEP 2004 HIGHEST RN 744786-72-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

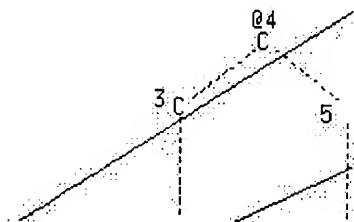
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

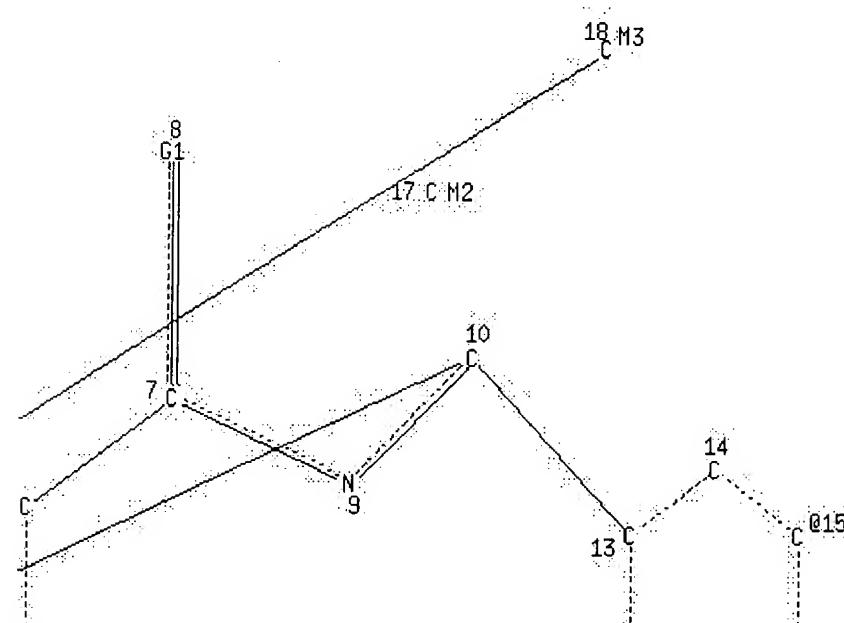
Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

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L6 HAS NO ANSWERS
L6      STR
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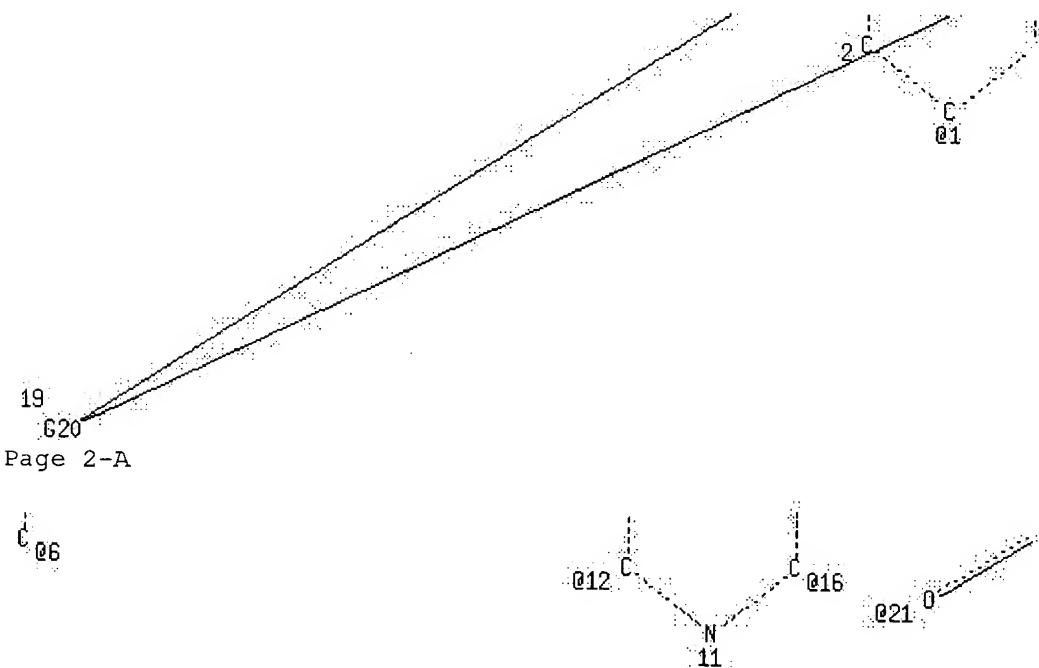
Page 1-A



Page 1-B

22
Ak

Page 1-C



N @20
Page 2-B

@6

Page 2-C

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VPA 20-1/4/6 S

h

eb c

g cg b cg

eb

VPA 21-12/15/16 S

NODE ATTRIBUTES:

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HCOUNT IS M3      AT  18
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NSPEC  IS R       AT   2
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DEFAULT ECLEVEL IS LIMITED

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GRAPH ATTRIBUTES:

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RSPEC I
NUMBER OF NODES IS  24

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STEREO ATTRIBUTES: NONE

=> s 16

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SAMPLE SCREEN SEARCH COMPLETED -      97 TO ITERATE

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100.0% PROCESSED      97 ITERATIONS          0 ANSWERS
SEARCH TIME: 00.00.01

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FULL FILE PROJECTIONS: ONLINE  **COMPLETE**
                      BATCH   **COMPLETE**
PROJECTED ITERATIONS:    1350 TO     2530
PROJECTED ANSWERS:        0 TO      0

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L7 0 SEA SSS SAM L6

=> s 16 full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y

FULL SEARCH INITIATED 20:37:24 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 2062 TO ITERATE

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100.0% PROCESSED      2062 ITERATIONS
SEARCH TIME: 00.00.01

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4 ANSWERS

L8 4 SEA SSS FUL L6

=> file hcaplus

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| FULL ESTIMATED COST | 155.42 | 321.11 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | 0.00 | -0.70 |

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FILE COVERS 1907 - 15 Sep 2004 VOL 141 ISS 12
 FILE LAST UPDATED: 14 Sep 2004 (20040914/ED)

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=> s 18

L9 2 L8

=> d his

(FILE 'HOME' ENTERED AT 20:32:06 ON 15 SEP 2004)

FILE 'REGISTRY' ENTERED AT 20:32:11 ON 15 SEP 2004

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| L2 | 0 S L1 |
| L3 | 1 S L1 FULL |

FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004

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|----|--------|

FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004

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| L5 | 0 S L3 |
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FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004

| | |
|----|--------------------|
| L6 | STRUCTURE UPLOADED |
| L7 | 0 S L6 |
| L8 | 4 S L6 FULL |

FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004

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|----|--------|

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L10 1 L9 NOT L4

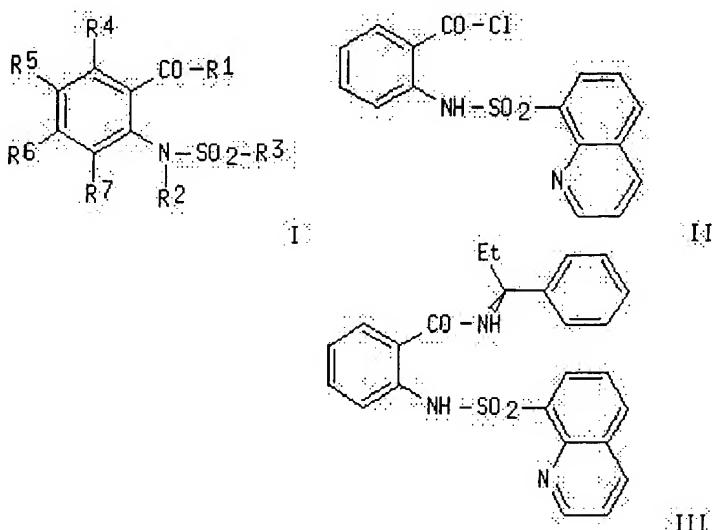
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L10 ANSWER 1 OF 1 HCPLUS COPYRIGHT 2004 ACS on STN

Full Editing
 Text References

ACCESSION NUMBER: 2002:964322 HCPLUS
 DOCUMENT NUMBER: 138:24550
 TITLE: Preparation of anthranilic acid amides as antiarrhythmics
 INVENTOR(S): Brendel, Joachim; Boehme, Thomas; Peukert, Stefan; Kleemann, Heinz-Werner
 PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
 SOURCE: PCT Int. Appl., 102 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-------------------------|------------|
| <u>WO 2002100825</u> | A2 | 20021219 | <u>WO 2002-EP5956</u> | 20020531 |
| <u>WO 2002100825</u> | A3 | 20031211 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| <u>DE 10128331</u> | A1 | 20021219 | <u>DE 2001-10128331</u> | 20010612 |
| <u>EE 200300558</u> | A | 20040216 | <u>EE 2003-558</u> | 20020531 |
| <u>EP 1399423</u> | A2 | 20040324 | <u>EP 2002-745333</u> | 20020531 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| <u>BR 2002010374</u> | A | 20040713 | <u>BR 2002-10374</u> | 20020531 |
| <u>US 2003114499</u> | A1 | 20030619 | <u>US 2002-166595</u> | 20020612 |
| <u>PRIORITY APPLN. INFO.:</u> | | | <u>DE 2001-10128331</u> | A 20010612 |
| OTHER SOURCE(S): GI | | | <u>WO 2002-EP5956</u> | W 20020531 |



AB Title compds. I [R1 = NR8-C(R9)(R10)-A-O-E-R11, NR8-C(R9)(R12)-A-D-E-R11, NR13-C(R9)(R10)-A-D-E-R11, etc.; A = CnH2n; n = 0-5; D = bond, O; E = CmH2m; m = 0-5; R8 = H, alkyl, CpH2p-R14; p = 0-5; R14 = (un)substituted Ph, naphthyl, heteroaryl, etc.; R9 = H, alkyl; R10 = H, alkyl, (un)substituted Ph, etc.; R11 = cycloalkyl, (un)substituted Ph, naphthyl, etc.; R12 = alkyl, alkynyl, cycloalkyl, etc.; R13 = CpH2p-R14; R2 = H, alkyl; R3 = (un)substituted heteroaryl; R4, R5, R6, R7 = H, halo, CF₃, etc.] and their pharmaceutically acceptable salts were prepd. For example, coupling of acid chloride II, e.g., prepd. from anthranilic acid in 2-steps, and (S)-1-phenylpropylamine afforded amide III. Compds. I act upon the Kv1.5 potassium channel and inhibit a potassium flow described as ultra-rapidly activating delayed rectifier in the human cardiac atrium.

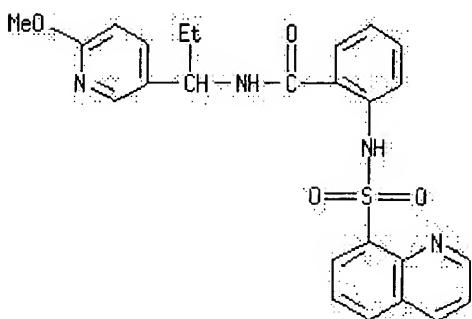
IT 478263-77-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; prepn. of anthranilic acid amides as antiarrhythmics)

RN 478263-77-3 HCAPLUS

CN Benzamide, N-[1-(6-methoxy-3-pyridinyl)propyl]-2-[(8-quinolinylsulfonyl)amino]- (9CI) (CA INDEX NAME)



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COST IN U.S. DOLLARS

SINCE FILE TOTAL:

FULL ESTIMATED COST

ENTRY SESSION
7-12 200-02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

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eh

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 FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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=> ~~s his~~

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FILE 'REGISTRY' ENTERED AT 20:32:11 ON 15 SEP 2004

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|----|--------------------|
| L1 | STRUCTURE UPLOADED |
| L2 | 0 S L1 |
| L3 | 1 S L1 FULL |

FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004

| | |
|----|--------|
| L4 | 1 S L3 |
|----|--------|

FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004

| | |
|----|--------|
| L5 | 0 S L3 |
|----|--------|

FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004

| | |
|----|--------------------|
| L6 | STRUCTURE UPLOADED |
| L7 | 0 S L6 |
| L8 | 4 S L6 FULL |

FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004

| | |
|-----|---------------|
| L9 | 2 S L8 |
| L10 | 1 S L9 NOT L4 |

FILE 'CAOLD' ENTERED AT 20:37:49 ON 15 SEP 2004

=> ~~s 18~~
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=> ~~file hcaplus~~
 COST IN U.S. DOLLARS

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

CA SUBSCRIBER PRICE

| | SINCE FILE ENTRY | TOTAL SESSION |
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| | 0.00 | -1.40 |

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FILE COVERS 1907 - 15 Sep 2004 VOL 141 ISS 12
 FILE LAST UPDATED: 14 Sep 2004 (20040914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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    15 POTASSIUMS
  542008 POTASSIUM
    (POTASSIUM OR POTASSIUMS)
  307634 CHANNEL?
L12      82 ANTIARRHYTHMIC? (W) POTASSIUM (W) CHANNEL?
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  893658 INHIBITOR?
L13      13 L12 AND INHIBITOR?
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  1757748 REVIEW/DT
L14      2 L13 AND REVIEW/DT
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L14 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Summary
 Text References

| | |
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| ACCESSION NUMBER: | 2002:949932 HCAPLUS |
| DOCUMENT NUMBER: | 138:19049 |
| TITLE: | The immediate future for the medical treatment of atrial fibrillation |
| AUTHOR(S): | Pedersen, Ole Dyg; Brendorp, Bente; Kober, Lars; Torp-Pedersen, Christian |
| CORPORATE SOURCE: | Department of Cardiology, Gentofte University Hospital, Hellerup, 2100, Den. |
| SOURCE: | Expert Opinion on Emerging Drugs (2002), 7(2), 259-268 |
| PUBLISHER: | Ashley Publications Ltd. |
| DOCUMENT TYPE: | Journal; General Review |
| LANGUAGE: | English |
| AB | A review. Atrial fibrillation is the most commonly sustained cardiac arrhythmia and a common reason for mortality and morbidity. Atrial |

fibrillation causes disease for three reasons: (i) the ventricular rate is often high, which leads to symptoms ranging from discomfort to life threatening heart failure; (ii) the rhythm causes loss of atrioventricular synchrony, which reduces diastolic filling and may lead to heart failure; and (iii) atrial contraction is lost leading to stagnant blood that again may lead to atrial thrombi and peripheral embolism. Thus, the treatment of atrial fibrillation is focused on the maintenance of sinus rhythm, rate control and prevention of embolism. For the maintenance of sinus rhythm, all drugs under current development are potassium channel blockers; the so-called class III anti-arrhythmic drugs. Those which have been further investigated appear to be valuable for maintenance of sinus rhythm but all carry a significant risk of pro-arrhythmia, in particular Torsade de Pointe ventricular tachycardia. Rate control has been a focus of treatment for many years and several very old drugs, including digoxin, are used for this. There is, to the author's knowledge, no current effort for evaluating new drugs for this indication. Prevention of embolism has for many years been obtained with vitamin K antagonists for which the clin. evidence is overwhelming. Previous attempts to replace vitamin K antagonists with aspirin have not been fruitful. A large no. of newer anticoagulation regimes are in development, but to the author's knowledge only a single thrombin **inhibitor** is actively being developed for atrial fibrillation.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 2 HCPLUS COPYRIGHT 2004 ACS on STN

Full SIFTED
 Text References

ACCESSION NUMBER: 2000:304412 HCPLUS
 DOCUMENT NUMBER: 132:302872
 TITLE: Antiarrhythmic pharmacotherapy for the 21st century.
 Development of new K⁺ channel blockers
 AUTHOR(S): Nakaya, Haruaki
 CORPORATE SOURCE: Dep. Pharmacol., Chiba Univ. Sch. Med., Japan
 SOURCE: Saishin Igaku (2000), 55(5), 1010-1016
 CODEN: SAIGAK; ISSN: 0370-8241
 PUBLISHER: Saishin Igakusha
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A review with 17 refs., on the structure and functional diversity of myocardial K⁺ channels, **inhibitory** effects of class III antiarrhythmic drugs on the K⁺ channels, ideal K⁺ channel blockers, and present status and future prospects of K⁺ channel blockers.

=> & his

(FILE 'HOME' ENTERED AT 20:32:06 ON 15 SEP 2004)

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 L3 1 S L1 FULL

FILE 'HCPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004
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FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
 L5 0 S L3

FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004
L6 STRUCTURE uploaded
L7 0 S L6
L8 4 S L6 FULL

FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004
L9 2 S L8
L10 1 S L9 NOT L4

FILE 'CAOLD' ENTERED AT 20:37:49 ON 15 SEP 2004
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L14 2 S L13 AND REVIEW/DT

=> s l12 and block?
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=> s l15 and review/dt
1757748 REVIEW/DT
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L17 12 L16 NOT L13

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L17 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full
Text

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| ACCESSION NUMBER: | 2003:778983 HCAPLUS |
| DOCUMENT NUMBER: | 140:138512 |
| TITLE: | Blockers of the Kv1.5 channel for the treatment of atrial arrhythmias |
| AUTHOR(S): | Brendel, Joachim; Peukert, Stefan |
| CORPORATE SOURCE: | Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany |
| SOURCE: | Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(3), 273-287 |
| PUBLISHER: | Bentham Science Publishers Ltd. |
| DOCUMENT TYPE: | Journal; General Review |
| LANGUAGE: | English |
| AB | A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs, there is a medical need for safer and more efficient antiarrhythmic treatment. Compds. that act atrial selectively without prolonging the QTc-time and without neg. inotropy to terminate and / or prevent atrial arrhythmias would be of high interest. In this context, the voltage-gated potassium channel Kv1.5 is regarded as a promising target to achieve atrial selectivity, which in turn would be assocd. with fewer side effects than classical antiarrhythmics. This review summarizes patents and other publications on compds. which show this novel mode of action. The chem., selectivity and structure-activity data disclosed in the literature are discussed in light of recent work demonstrating the antiarrhythmic efficacy of Kv1.5 blockers <i>in vivo</i> . Several studies in pig, dog or goat models have confirmed their proposed atrial selective antiarrhythmic |

effect in vivo. Most of the more intensively characterized Kv1.5 blockers have turned out not to be selective but also block other ion channels. Based on the currently available data it seems that addnl. inhibition of Kv4.3 and KACH is beneficial for the desired antiarrhythmic effect or at least does not hamper the atrial selectivity of a Kv1.5 blocker. Significant block of IK1, HERG or sodium channels, however, clearly leads to loss of atrial selectivity and increases the risk of lethal ventricular proarrhythmia.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full References
 Text

ACCESSION NUMBER: 2003:12740 HCAPLUS
 DOCUMENT NUMBER: 138:378418
 TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
 AUTHOR(S): Brendel, Joachim; Peukert, Stefan
 CORPORATE SOURCE: Medicinal Chemistry, G878, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
 SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(11), 1589-1598
 PUBLISHER: EOTPEG; ISSN: 1354-3776
 DOCUMENT TYPE: Ashley Publications Ltd.
 LANGUAGE: Journal; General Review
 English
 AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs there is a medical need for safer and more efficient treatments. The voltage-gated potassium channel Kv1.5 is regarded as a promising target for the development of new atrial selective drugs with fewer side effects. This review summarizes patents claiming such compds. The chem. and biol. data disclosed in these patents are discussed in light of recent work demonstrating the antiarrhythmic effects of Kv1.5 blockers in vivo.
 REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full References
 Text

ACCESSION NUMBER: 2002:290489 HCAPLUS
 DOCUMENT NUMBER: 137:179233
 TITLE: Animal models of lethal arrhythmias
 AUTHOR(S): Billman, George E.
 CORPORATE SOURCE: Department of Physiology and Cell Biology, The Ohio State University, Columbus, OH, 43210-1218, USA
 SOURCE: Drug Development Research (2002), 55(1), 59-72
 PUBLISHER: Wiley-Liss, Inc.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States. Yet, despite the enormity of this problem, the development of safe and effective antiarrhythmic agents remains elusive. Indeed, several class I (encainide and flecainide) and class III (d-sotalol) drugs have actually been shown to increase, rather

than decrease, the risk of arrhythmic death in patients recovering from myocardial infarction. The identification of effective antiarrhythmic agents is critically dependent on the use of appropriate animal models of human disease. In particular, myocardial ischemia may be an important determinant for the development of the life-threatening ventricular arrhythmias. For example, preclin. studies demonstrate that many drugs that prevent arrhythmias induced by programmed elec. stimulation fail to prevent ventricular fibrillation provoked by ischemia in the same animals. Thus, one would predict that animal models in which lethal arrhythmias are induced by myocardial ischemia would be the most effective tools for the identification of potential antiarrhythmic medications. This review first evaluates several animal models of lethal ventricular arrhythmias with particular emphasis placed on canine models. Then it closes with a brief discussion of ATP-sensitive potassium-channel antagonists as an example of antiarrhythmic drugs that may act selectively on the ischemic myocardium.

REFERENCE COUNT: 160 THERE ARE 160 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full ~~Abstract~~
 Text References

ACCESSION NUMBER: 2002:41806 HCAPLUS
 DOCUMENT NUMBER: 137:149522
 TITLE: Clamikalant sodium: Antiarrhythmic KATP channel blocker
 AUTHOR(S): Mealy, N. E.; Martin, L.; Castaner, J.
 CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
 SOURCE: Drugs of the Future (2001), 26(10), 951-956
 CODEN: DRFUD4; ISSN: 0377-8282
 PUBLISHER: Prous Science
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review discussing the synthesis, pharmacol. actions, toxicol., pharmacokinetics and metab., and clin. studies of clamikalant sodium. Clamikalant sodium, which is currently in phase II clin. trials, was discovered to **block** cardiac ATP-sensitive potassium channels more effectively than pancreatic and vascular channels.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full ~~Abstract~~
 Text References

ACCESSION NUMBER: 2001:588455 HCAPLUS
 DOCUMENT NUMBER: 136:288373
 TITLE: IKs channel blockers: potential antiarrhythmic agents
 AUTHOR(S): Gerlach, U.
 CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
 SOURCE: Drugs of the Future (2001), 26(5), 473-484
 CODEN: DRFUD4; ISSN: 0377-8282
 PUBLISHER: Prous Science
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review, with refs., discusses the different functions of IKs channel blockers, with emphasis on cardiac arrhythmias. Topics covered include ion channels in the heart; ion channel blockers as antiarrhythmic agents; mol. structure and function of the IKs channel; tissue species distribution of the IKs channel; selective IKs channel blockers; and

drugs with IKs **blocking** activity as an addnl. effect

REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L17 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full
Text

ACCESSION NUMBER: 2000:191638 HCPLUS
DOCUMENT NUMBER: 133:68210
TITLE: Nifekalant, Mitsui
AUTHOR(S): Zaza, Antonio
CORPORATE SOURCE: University of Milan, Milan, 20133, Italy
SOURCE: Current Opinion in Cardiovascular, Pulmonary & Renal
Investigational Drugs (2000), 2(1), 86-94
CODEN: CCPRFX; ISSN: 1464-8482
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 120 refs., of the pharmacol. of nifekalant, a Class III (nonselective K⁺ channel **blocker**) antiarrhythmic agent that lacks **β -blocking** activity.

REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L17 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full
Text
References

ACCESSION NUMBER: 1997:185324 HCAPLUS
DOCUMENT NUMBER: 126:194770
TITLE: Antiarrhythmic effects of K channel blockers
AUTHOR(S): Hagiwara, Nobuhisa; Kajimoto, Katsuya; Sakai, Rieko;
Kasanuki, Hiroshi; Hosoda, Saichi
CORPORATE SOURCE: Dep. Cardiovascular Medicine, Heart Inst. of Japan,
Japan
SOURCE: Kokyu to Junkan (1997), 45(2), 137-143
PUBLISHER: CODEN: KOJUA9; ISSN: 0452-3458
DOCUMENT TYPE: Igaku Shoin
LANGUAGE: Journal; General Review
Japanese

AB A review, with 17 refs., discussing the antiarrhythmic effects of K channel blockers.

L17 ANSWER 8 OF 12 HCPLUS COPYRIGHT 2004 ACS on STN

Full Text

ACCESSION NUMBER: 1995:227957 HCAPLUS
DOCUMENT NUMBER: 122:144
TITLE: Potassium channel blockers as antiarrhythmic drug.
AUTHOR(S): Colatsky, Thomas J.; Argentieri, Thomas M.
CORPORATE SOURCE: Division Cardiovascular Diseases Diabetes,
Wyeth-Ayerst Research, Princeton, NJ, 08543, USA
SOURCE: Drug Development Research (1994), 33(3), 235-49
PUBLISHER: CODEN: DDREDK; ISSN: 0272-4391

PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with >100 refs. Selective prolongation of cardiac repolarization
is an effective means of suppressing a variety of cardiac arrhythmias.

particularly those arising from a re-entrant mechanism. Over the past several years, a variety of novel compds. have been discovered that increase cardiac action potential duration without slowing conduction. Most of these agents (e.g., dofetilide, E-4031, MK-499) act by selectively **blocking** the rapidly activating component of delayed rectification (IKr), although some (e.g., ibutilide, azimilide, terikalant) have been proposed to work via alternate mechanisms. While the overall efficacy of these agents against tachyarrhythmias appears to be greater than obtained for the sodium channels **blockers**, primary concerns remain about the ability of these agents to prolong repolarization at fast heart rates (i.e., reverse use-dependence) and to exert proarrhythmic effects at slow heart rates (i.e., torsade de pointes). The limited clin. results obtained to date suggest that these potential limitations may be less important than previously thought, although clear pharmacodynamic differences among the various agents are beginning to emerge. While the effects of some class III agents on repolarization and refractoriness are clearly attenuated at rapid cycle lengths (e.g., sotalol, d-sotalol), the effects of others appear to be largely rate-independent, at least down to cycles as short as 350 ms. Also, the currently available data suggest that the risk of serious proarrhythmia may be lower (1-3%) and considerably more predictable than that seen during treatment with the class I agents. In summary, the rational design of selective **blockers** of cardiac K channels for development as antiarrhythmic drugs appears to have been relatively successful and continues to show considerable promise as a therapeutic approach.

L17 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 1994:260301 HCAPLUS
 DOCUMENT NUMBER: 120:260301
 TITLE: Potassium channel **blockade** as an antiarrhythmic principle
 AUTHOR(S): Mortensen, Elin; Yang, Tao; Refsum, Helge
 CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Tromso, N-9037, Norway
 SOURCE: Cardiovascular Drug Reviews (1993), 11(3), 370-84
 DOCUMENT TYPE: CODEN: CDREEA; ISSN: 0897-5957
 LANGUAGE: Journal; General Review
 English
 AB A review with 89 refs. Cardiac K⁺ channels and their physiol. role, antiarrhythmic mechanisms of K⁺ channel **blockers**, and K⁺ channel **blockade** in myocardial ischemia, heart failure, pos. inotropy, and heart rate are discussed.

L17 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 1993:204515 HCAPLUS
 DOCUMENT NUMBER: 118:204515
 TITLE: Recent advances in antiarrhythmic therapy: Potassium channel antagonists
 AUTHOR(S): Cimini, Madeline G.; Gibson, J. Kenneth
 CORPORATE SOURCE: Upjohn Lab., Kalamazoo, MI, 49001, USA
 SOURCE: Annual Reports in Medicinal Chemistry (1992), 27, 89-98
 DOCUMENT TYPE: CODEN: ARMCBI; ISSN: 0065-7743
 LANGUAGE: Journal; General Review
 English
 AB A review with 92 refs.

L17 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Search
 Text References

ACCESSION NUMBER: 1990:171527 HCAPLUS
 DOCUMENT NUMBER: 112:171527
 TITLE: Potassium channels in cardiac arrhythmias: focus on antiarrhythmic drug action
 AUTHOR(S): Rials, Seth J.; Friehling, Ted D.; Marinchak, Roger A.; Kowey, Peter R.
 CORPORATE SOURCE: Cardiac Arrhythmia Serv., Med. Coll. Pennsylvania, Philadelphia, PA, 19129, USA
 SOURCE: Progress in Clinical and Biological Research (1990), Volume Date 1988, 334(Potassium Channels), 111-21
 DOCUMENT TYPE: CODEN: PCBRD2; ISSN: 0361-7742
 LANGUAGE: Journal; General Review
 English
 AB A review with 26 refs.

L17 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Search
 Text References

ACCESSION NUMBER: 1990:151089 HCAPLUS
 DOCUMENT NUMBER: 112:151089
 TITLE: Potassium channels as targets for antiarrhythmic drug action
 AUTHOR(S): Colatsky, T. J.; Follmer, C. H.
 CORPORATE SOURCE: Div. Exp. Ther., Wyeth-Ayerst Res., Princeton, NJ, 08543, USA
 SOURCE: Drug Development Research (1990), 19(2), 129-40
 DOCUMENT TYPE: CODEN: DDREDK; ISSN: 0272-4391
 LANGUAGE: Journal; General Review
 English
 AB A review with approx. 55 refs. on the role of K channel in the pharmacol. of antiarrhythmic agents. The class I agents have been shown to **block** cardiac sodium channels in a use-dependent manner, and the kinetics and potency of sodium channel **block** correlated with mol. wt. and lipid solv. of drug. The class IA agents, like quinidine, which increase cardiac action potential duration and refractory period in addn. to their effects on conduction, also appear to have potent **blocking** actions on the potassium channels responsible for repolarization in myocardial cells, whereas the class IB agents, like lidocaine, shorten action potential duration and are relatively specific in their **block** of sodium channels. In contrast, class III agents, which prolong the action potential without slowing conduction, appear to exert their primary **blocking** action on the potassium channel only. Conversion from class I to class III electrophysiol. profiles can be achieved by the substitution of electron-withdrawing groups (e.g., NO₂) in place of electron-donating groups (e.g., NH₂) on the arom. portion of the basic local anesthetic pharmacophore. Class III agents appear to be most effective against ventricular fibrillation and ventricular tachycardia due to re-entry, but are generally without activity in the 24 h Harris dog arrhythmia model.

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(FILE 'HOME' ENTERED AT 20:32:06 ON 15 SEP 2004)

FILE 'REGISTRY' ENTERED AT 20:32:11 ON 15 SEP 2004

L1 STRUCTURE uploaded
 L2 O S LI

h eb c g cg b cg

eb

L3 1 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004
1 S L3

L5 FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
0 S I.3

L6 FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004
L7 STRUCTURE UPLOADED
L8 O S L6
L8 4 S L6 FULL

FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004
L9 2 S L8
L10 1 S L9 NOT L4

L11 FILE 'CAOLD' ENTERED AT 20:37:49 ON 15 SEP 2004
O S L8

FILE 'HCAPLUS' ENTERED AT 20:39:28 ON 15 SEP 2004
L12 82 S ANTIARRHYTHMIC? () POTASSIUM () CHANNEL?
L13 13 S L12 AND INHIBITOR?
L14 2 S L13 AND REVIEW/DT
L15 68 S L12 AND BLOCK?
L16 14 S L15 AND REVIEW/DT
L17 12 S L16 NOT L13

=> s l12 and blocker?
54106 BLOCKER?
L18 57 L12 AND BLOCKER?

=> s L18 and review/dt
1757748 REVIEW/DT
L19 13 L18 AND REVIEW/DT

=> d 119, bibb abs, i=13

L19 ANSWER 1 OF 13 HCPLUS COPYRIGHT 2004 ACS on STN
Full

ACCESSION NUMBER: 2003:778983 HCAPLUS
DOCUMENT NUMBER: 140:138512
TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
AUTHOR(S): Brendel, Joachim; Peukert, Stefan
CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH,
Frankfurt/Main, D-65926, Germany
SOURCE: Current Medicinal Chemistry: Cardiovascular &
Hematological Agents (2003), 1(3), 273-287
CODEN: CMCCDP; ISSN: 1568-0169
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs, there is a medical need for safer and more efficient antiarrhythmic treatment. Compds. that act atrial selectively without prolonging the QTc-time and without neg. inotropy to terminate and / or prevent atrial arrhythmias would be of high interest. In this context, the voltage-gated potassium

channel Kv1.5 is regarded as a promising target to achieve atrial selectivity, which in turn would be assocd. with fewer side effects than classical antiarrhythmics. This review summarizes patents and other publications on compds. which show this novel mode of action. The chem., selectivity and structure-activity data disclosed in the literature are discussed in light of recent work demonstrating the antiarrhythmic efficacy of Kv1.5 **blockers** in vivo. Several studies in pig, dog or goat models have confirmed their proposed atrial selective antiarrhythmic effect in vivo. Most of the more intensively characterized Kv1.5 **blockers** have turned out not to be selective but also block other ion channels. Based on the currently available data it seems that addnl. inhibition of Kv4.3 and KACH is beneficial for the desired antiarrhythmic effect or at least does not hamper the atrial selectivity of a Kv1.5 **blocker**. Significant block of IK1, HERG or sodium channels, however, clearly leads to loss of atrial selectivity and increases the risk of lethal ventricular proarrhythmia.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Search
 Text References

ACCESSION NUMBER: 2003:12740 HCAPLUS
 DOCUMENT NUMBER: 138:378418
 TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
 AUTHOR(S): Brendel, Joachim; Peukert, Stefan
 CORPORATE SOURCE: Medicinal Chemistry, G878, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
 SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(11), 1589-1598
 PUBLISHER: CODEN: EOTPEG; ISSN: 1354-3776
 DOCUMENT TYPE: Ashley Publications Ltd.
 LANGUAGE: Journal; General Review
 English

AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs there is a medical need for safer and more efficient treatments. The voltage-gated potassium channel Kv1.5 is regarded as a promising target for the development of new atrial selective drugs with fewer side effects. This review summarizes patents claiming such compds. The chem. and biol. data disclosed in these patents are discussed in light of recent work demonstrating the antiarrhythmic effects of Kv1.5 **blockers** in vivo.

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Search
 Text References

ACCESSION NUMBER: 2002:949932 HCAPLUS
 DOCUMENT NUMBER: 138:19049
 TITLE: The immediate future for the medical treatment of atrial fibrillation
 AUTHOR(S): Pedersen, Ole Dyg; Brendorp, Bente; Kober, Lars;
 Torp-Pedersen, Christian
 CORPORATE SOURCE: Department of Cardiology, Gentofte University Hospital, Hellerup, 2100, Den.
 SOURCE: Expert Opinion on Emerging Drugs (2002), 7(2), 259-268
 CODEN: EOEDA3

PUBLISHER: Ashley Publications Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. Atrial fibrillation is the most commonly sustained cardiac arrhythmia and a common reason for mortality and morbidity. Atrial fibrillation causes disease for three reasons: (i) the ventricular rate is often high, which leads to symptoms ranging from discomfort to life threatening heart failure; (ii) the rhythm causes loss of atrioventricular synchrony, which reduces diastolic filling and may lead to heart failure; and (iii) atrial contraction is lost leading to stagnant blood that again may lead to atrial thrombi and peripheral embolism. Thus, the treatment of atrial fibrillation is focused on the maintenance of sinus rhythm, rate control and prevention of embolism. For the maintenance of sinus rhythm, all drugs under current development are potassium channel blockers; the so-called class III anti-arrhythmic drugs. Those which have been further investigated appear to be valuable for maintenance of sinus rhythm but all carry a significant risk of pro-arrhythmia, in particular Torsade de Pointe ventricular tachycardia. Rate control has been a focus of treatment for many years and several very old drugs, including digoxin, are used for this. There is, to the author's knowledge, no current effort for evaluating new drugs for this indication. Prevention of embolism has for many years been obtained with vitamin K antagonists for which the clin. evidence is overwhelming. Previous attempts to replace vitamin K antagonists with aspirin have not been fruitful. A large no. of newer anticoagulation regimes are in development, but to the author's knowledge only a single thrombin inhibitor is actively being developed for atrial fibrillation.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 13 HCPLUS COPYRIGHT 2004 ACS on STN

Full Text SEARCHED
 PUBLISHER

ACCESSION NUMBER: 2002:290489 HCPLUS
 DOCUMENT NUMBER: 137:179233
 TITLE: Animal models of lethal arrhythmias
 AUTHOR(S): Billman, George E.
 CORPORATE SOURCE: Department of Physiology and Cell Biology, The Ohio State University, Columbus, OH, 43210-1218, USA
 SOURCE: Drug Development Research (2002), 55(1), 59-72
 CODEN: DDREDK; ISSN: 0272-4391
 PUBLISHER: Wiley-Liss, Inc.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States. Yet, despite the enormity of this problem, the development of safe and effective antiarrhythmic agents remains elusive. Indeed, several class I (encainide and flecainide) and class III (d-sotalol) drugs have actually been shown to increase, rather than decrease, the risk of arrhythmic death in patients recovering from myocardial infarction. The identification of effective antiarrhythmic agents is critically dependent on the use of appropriate animal models of human disease. In particular, myocardial ischemia may be an important determinant for the development of the life-threatening ventricular arrhythmias. For example, preclin. studies demonstrate that many drugs that prevent arrhythmias induced by programmed elec. stimulation fail to prevent ventricular fibrillation provoked by ischemia in the same animals. Thus, one would predict that animal models in which lethal arrhythmias are

induced by myocardial ischemia would be the most effective tools for the identification of potential antiarrhythmic medications. This review first evaluates several animal models of lethal ventricular arrhythmias with particular emphasis placed on canine models. Then it closes with a brief discussion of ATP-sensitive potassium-channel antagonists as an example of antiarrhythmic drugs that may act selectively on the ischemic myocardium.

REFERENCE COUNT: 160 THERE ARE 160 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 2002:41806 HCAPLUS
 DOCUMENT NUMBER: 137:149522
 TITLE: Clamikalant sodium: Antiarrhythmic KATP channel blocker
 AUTHOR(S): Mealy, N. E.; Martin, L.; Castaner, J.
 CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
 SOURCE: Drugs of the Future (2001), 26(10), 951-956
 CODEN: DRFUD4; ISSN: 0377-8282
 PUBLISHER: Prous Science
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review discussing the synthesis, pharmacol. actions, toxicol., pharmacokinetics and metab., and clin. studies of clamikalant sodium. Clamikalant sodium, which is currently in phase II clin. trials, was discovered to block cardiac ATP-sensitive potassium channels more effectively than pancreatic and vascular channels.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 2001:588455 HCAPLUS
 DOCUMENT NUMBER: 136:288373
 TITLE: IKs channel blockers: potential antiarrhythmic agents
 AUTHOR(S): Gerlach, U.
 CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
 SOURCE: Drugs of the Future (2001), 26(5), 473-484
 CODEN: DRFUD4; ISSN: 0377-8282
 PUBLISHER: Prous Science
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review, with refs., discusses the different functions of IKs channel blockers, with emphasis on cardiac arrhythmias. Topics covered include ion channels in the heart; ion channel blockers as antiarrhythmic agents; mol. structure and function of the IKs channel; tissue species distribution of the IKs channel; selective IKs channel blockers; and drugs with IKs blocking activity as an addnl. effect.

REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 2000:304412 HCAPLUS

DOCUMENT NUMBER: 132:302872
 TITLE: Antiarrhythmic pharmacotherapy for the 21st century.
 AUTHOR(S): Development of new K⁺ channel blockers
 CORPORATE SOURCE: Nakaya, Haruaki
 SOURCE: Dep. Pharmacol., Chiba Univ. Sch. Med., Japan
 Saishin Igaku (2000), 55(5), 1010-1016
 CODEN: SAIGAK; ISSN: 0370-8241
 PUBLISHER: Saishin Igakusha
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A review with 17 refs., on the structure and functional diversity of myocardial K⁺ channels, inhibitory effects of class III antiarrhythmic drugs on the K⁺ channels, ideal K⁺ channel blockers, and present status and future prospects of K⁺ channel blockers.

L19 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 2000:191638 HCAPLUS
 DOCUMENT NUMBER: 133:68210
 TITLE: Nifekalant, Mitsui
 AUTHOR(S): Zaza, Antonio
 CORPORATE SOURCE: University of Milan, Milan, 20133, Italy
 SOURCE: Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs (2000), 2(1), 86-94
 CODEN: CCPRFX; ISSN: 1464-8482
 PUBLISHER: PharmaPress Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review, with 120 refs., of the pharmacol. of nifekalant, a Class III (nonselective K⁺ channel blocker) antiarrhythmic agent that lacks β-blocking activity.
 REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L19 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 1997:185324 HCAPLUS
 DOCUMENT NUMBER: 126:194770
 TITLE: Antiarrhythmic effects of K channel blockers
 AUTHOR(S): Hagiwara, Nobuhisa; Kajimoto, Katsuya; Sakai, Rieko; Kasanuki, Hiroshi; Hosoda, Saichi
 CORPORATE SOURCE: Dep. Cardiovascular Medicine, Heart Inst. of Japan, Japan
 SOURCE: Kokyu to Junkan (1997), 45(2), 137-143
 CODEN: KOJUA9; ISSN: 0452-3458
 PUBLISHER: Igaku Shoin
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A review, with 17 refs., discussing the antiarrhythmic effects of K channel blockers.

L19 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 1995:227957 HCAPLUS
 DOCUMENT NUMBER: 122:144
 TITLE: Potassium channel blockers as antiarrhythmic drugs

AUTHOR(S): Colatsky, Thomas J.; Argentieri, Thomas M.
 CORPORATE SOURCE: Division Cardiovascular Diseases Diabetes,
 Wyeth-Ayerst Research, Princeton, NJ, 08543, USA
 SOURCE: Drug Development Research (1994), 33(3), 235-49
 CODEN: DDREDK; ISSN: 0272-4391
 PUBLISHER: Wiley-Liss
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review with >100 refs. Selective prolongation of cardiac repolarization is an effective means of suppressing a variety of cardiac arrhythmias, particularly those arising from a re-entrant mechanism. Over the past several years, a variety of novel compds. have been discovered that increase cardiac action potential duration without slowing conduction. Most of these agents (e.g., dofetilide, E-4031, MK-499) act by selectively blocking the rapidly activating component of delayed rectification (IKr), although some (e.g., ibutilide, azimilide, terikalant) have been proposed to work via alternate mechanisms. While the overall efficacy of these agents against tachyarrhythmias appears to be greater than obtained for the sodium channels **blockers**, primary concerns remain about the ability of these agents to prolong repolarization at fast heart rates (i.e., reverse use-dependence) and to exert proarrhythmic effects at slow heart rates (i.e., torsade de pointes). The limited clin. results obtained to date suggest that these potential limitations may be less important than previously thought, although clear pharmacodynamic differences among the various agents are beginning to emerge. While the effects of some class III agents on repolarization and refractoriness are clearly attenuated at rapid cycle lengths (e.g., sotalol, d-sotalol), the effects of others appear to be largely rate-independent, at least down to cycles as short as 350 ms. Also, the currently available data suggest that the risk of serious proarrhythmia may be lower (1-3%) and considerably more predictable than that seen during treatment with the class I agents. In summary, the rational design of selective **blockers** of cardiac K channels for development as antiarrhythmic drugs appears to have been relatively successful and continues to show considerable promise as a therapeutic approach.

L19 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 1994:260301 HCAPLUS
 DOCUMENT NUMBER: 120:260301
 TITLE: Potassium channel blockade as an antiarrhythmic principle
 AUTHOR(S): Mortensen, Elin; Yang, Tao; Refsum, Helge
 CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Tromso, N-9037, Norway
 SOURCE: Cardiovascular Drug Reviews (1993), 11(3), 370-84
 CODEN: CDREEA; ISSN: 0897-5957
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review with 89 refs. Cardiac K⁺ channels and their physiol. role, antiarrhythmic mechanisms of K⁺ channel **blockers**, and K⁺ channel blockade in myocardial ischemia, heart failure, pos. inotropy, and heart rate are discussed.

L19 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Citations
 Text References

ACCESSION NUMBER: 1993:204515 HCAPLUS
 DOCUMENT NUMBER: 118:204515
 TITLE: Recent advances in antiarrhythmic therapy: Potassium

AUTHOR(S): channel antagonists
Cimini, Madeline G.; Gibson, J. Kenneth
CORPORATE SOURCE: Upjohn Lab., Kalamazoo, MI, 49001, USA
SOURCE: Annual Reports in Medicinal Chemistry (1992), 27,
89-98
DOCUMENT TYPE: CODEN: ARMCBI; ISSN: 0065-7743
Journal; General Review
LANGUAGE: English
AB A review with 92 refs.

L19 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full String
Text Reference

ACCESSION NUMBER: 1990:171527 HCAPLUS
DOCUMENT NUMBER: 112:171527
TITLE: Potassium channels in cardiac arrhythmias: focus on
antiarrhythmic drug action
AUTHOR(S): Rials, Seth J.; Friehling, Ted D.; Marinchak, Roger
A.; Kowey, Peter R.
CORPORATE SOURCE: Cardiac Arrhythmia Serv., Med. Coll. Pennsylvania,
Philadelphia, PA, 19129, USA
SOURCE: Progress in Clinical and Biological Research (1990),
Volume Date 1988, 334(Potassium Channels), 111-21
DOCUMENT TYPE: CODEN: PCBRD2; ISSN: 0361-7742
Journal; General Review
LANGUAGE: English
AB A review with 26 refs.

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USA. The antiarrhythmics of classes I and III customary at present reduce the reoccurrence rate of AF, but are only used restrictively because of their potential proarrhythmic side effects. There is therefore a great medical need for the development of better medicaments for the treatment of atrial arrhythmias (S.

- 5 Nattel, Am. Heart J. 130, 1995, 1094 - 1106; "Newer developments in the management of atrial fibrillation").

It has been shown that most supraventricular arrhythmias are subject to "reentry" excitation waves. Such reentries occur when the cardiac tissue possesses a slow

- 10 conductivity and at the same time very short refractory periods. The increase in the myocardial refractory period due to prolongation of the action potential is a recognized mechanism for ending arrhythmias or preventing their formation (T. J. Colatsky et al., Drug Dev. Res. 19, 1990, 129 - 140; "Potassium channels as targets for antiarrhythmic drug action"). The length of the action potential is
15 essentially determined by the extent of repolarizing K⁺ currents which flow out of the cell via various K⁺ channels. Particularly great importance is ascribed here to the "delayed rectifier" IK, which consists of 3 different components: IK_r, IK_s and IK_{ur}.

Most known class III antiarrhythmics (for example dofetilide, E4031 and d-sotalol)

- 20 mainly or exclusively block the rapidly activating potassium channel IK_r, which can be detected both in cells of the human ventricle and in the atrium. It has been shown, however, that these compounds have an increased proarrhythmic risk at low or normal heart rates, arrhythmias, which are described as "torsades de pointes", in particular being observed (D. M. Roden, Am. J. Cardiol. 72, 1993, 44B
25 - 49B; "Current status of class III antiarrhythmic drug therapy"). Beside this high and in some cases fatal risk at a low rate, a decrease in the activity under the conditions of tachycardia, in which the action is needed in particular, was found for the IK_r blockers ("negative use dependence").

- 30 The "particularly rapidly" activating and very slowly inactivating component of the delayed rectifier IK_{ur} (= ultra-rapidly activating delayed rectifier), which corresponds